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EXAMINER

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ART UNIT	PAPER NUMBER
1646	6

MERTZ, P.

DATE MAILED: 09/28/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 6-5-98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-19 is/are pending in the application.
Of the above, claim(s) 16-19 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1, 3, 6-15 is/are rejected.
☑ Claim(s) 2, 4-5 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-498/40511

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-15, drawn to a conjugate of a non-immunogenic toxin or therapeutic radionuclide and a cell-specific cytokine and a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α, classified in class 530, subclass 402.

II. Claims 16-19, drawn to a method of treating a malignancy by administering a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α and then administering to said subject therapeutically effective amount of a conjugate of onconase and IL-15, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the conjugate and fusion polypeptides can be used as antigen for antibody production.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject

matter as defined by MPEP § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

2. During a telephone conversation with Bernhard D. Saxe on 7/3/98, a provisional election was made with traverse to prosecute the invention of Group I (claims 1-15). Affirmation of this election must be made by applicant in responding to this Office action. Claims 16-19 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Specification

3. Since this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a) (1) and (a)(2). However, the specification fails to comply with one or more of the requirements of 37 CFR § 1.821 through 1.825 as follows: Specifically, no sequence listing has been provided which includes the amino acid sequence presented in the specification on page 13, line 6. Applicant needs to provide a computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are

present in the instant application and encompassed by these rules, a paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the copy of the paper and computer readable copies are the same and, where applicable, includes no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.821(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires that a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims where ever a reference is made to that sequence. For rules Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Claim Rejections - 35 USC § 112

4. Claims 8-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a fusion protein comprising a bispecific antibody that has a first specificity for CD20 and a second specificity for a region of IL-15α, does not reasonably provide enablement for a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell and a second specificity for a region of IL-15α. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 8 specifically recites that the cell marker is specific to a malignant cell, the target cells being B cells (claim 11), as disclosed in the specification. However, the specification is non-enabling for a fusion protein comprising a bispecific antibody that has a first specificity for a cell marker specific to a malignant cell, because there are no specific cell markers known that are specific to

malignant cells. Upon reviewing the art, none of the art of record disclose or suggest a molecule such as this with specificity for binding to specific markers only on malignant cells or only on malignant B cells, and neither does the instant specification, since the claims require specificity of binding only to malignant cells. Furthermore, the specific CD20 receptors are cell markers expressed on various B cells of the immune system, including pre-B cells, resting, activated and malignant B cells. In order to practice the invention the artisan would have to know how to deliver the therapeutic agent i.e. fusion protein selectively to malignant B cells without placing at risk all cells bearing CD40 receptors, since in the process of killing a large number of undesirably activated cells, if the therapeutic agent also killed most of the CD40 bearing cells responsible for the normal function of the immune system, the agent would not be useful in the claimed kit or for therapy. The specification neither teaches a method of targeting the sub-population of malignant cells nor provides evidence that such cells are on the whole more sensitive to the therapeutic agent and that routine administration of the fusion protein would yield acceptable results.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5a. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Verheul et al. (WO 92/00762).

Verheul et al teach a conjugate of a non-immunogenic toxin and a cell-specific cytokine such as IL-2 (see page 5, fourth and last paragraphs; and claims 1-16). Verheul also teaches a pharmaceutical composition comprising the conjugate (page 6, third paragraph). Therefore, the disclosure of Verheul et al anticipates claims 1 and 6.

5b. Claims 1, 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Mallinckrodt Medical, Inc. (WO 94/07535).

Mallinckrodt Medical, Inc. teach a conjugate of a therapeutic radionuclide and a cell-specific cytokine such as IL-2 (see page 2, last 3 lines; page 3, lines 1-8; page 5, lines 4-11). The reference also teaches a pharmaceutical composition comprising the conjugate (page 10, lines 10-12). Therefore, the disclosure of Mallinckrodt Medical, Inc anticipates claims 1, 6-7.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6a. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Verheul et al. (WO 92/00762) as applied to claims 1 and 6 above, and further in view of Anderson et al. (1995).

The disclosure of Verheul et al. has been set forth above (see paragraph 5a).Verheul et al. do not explicitly recite a conjugate of a non-immunogenic toxin and a cell-specific cytokine IL-15.

Anderson et al teach that the receptors for IL-2 and IL-15 share 2 subunits (the IL-2Rβ and -γ chains) that are essential for signal transduction and that the IL-15 specific α subunit was identified, cloned and shown to be structurally similar to IL-2Rα (see abstract, lines 1-8, page 29862, column 1). Anderson et al also teach that IL-15 shares biological activities with IL-2; such as the activation and proliferation of T cells and the costimulation of B cells with CD40 ligand (page 29862, column 2, first para, lines 1-4).

It would have been *prima facie* obvious at the time the invention was made to modify the conjugate of Verheul et al. by substitution of IL-2 in the conjugate with IL-15 as taught by Anderson et al with a reasonable expectation of success because Anderson et al teach that the cytokines IL-15 and IL-2 shares biological activities with IL-15. The motivation for the use of IL-15 as the cell-specific cytokine in the conjugate is provided by Verheul, which discloses that when the ligand chosen has binding activity for example, to the IL-2 receptor the targeted toxin molecules of the invention are suitable as therapeutics for autoimmune diseases in general and for rheumatoid arthritis in

particular (see page 4, first para). Furthermore, the targeted molecules may be used to remove IL-2 expressing haematopoietic cell leukemias, to induce specific tolerance in transplantation patients or in patients receiving treatment with an antibody of foreign origin.

Conclusion

7. No claim is allowed.

Claims 2, 4-5 are objected to for being dependent on a rejected base claim.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz

Prema Mertz Ph.D.
Patent Examiner
Art Unit 1646
September 16, 1998